United States Patent

Fitzmaurice et al.

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[45] ***Aug. 22, 1972**

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[54] **BIS-PHENOXY COMPOUNDS**

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[*] Notice: The portion of the term of this patent subsequent to Dec. 31, 1985, has been disclaimed.

[22] Filed: **Sept. 25, 1968**

[21] Appl. No.: **762,638**

Related U.S. Application Data

[62] Division of Ser. Nos. 536,281, March 22, 1966, Pat. No. 3,419,578, and Ser. No. 765,722, July 30, 1968.

[52] **U.S. Cl.** **260/592,** 167/54, 167/55, 167/65, 260/345.2, 260/340.6, 260/473, 260/520, 260/613, 424/10, 424/278

[51] **Int. Cl.** **C07c 49/78**

[58] **Field of Search** 260/592

[56] **References Cited**

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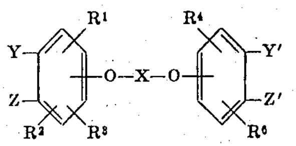
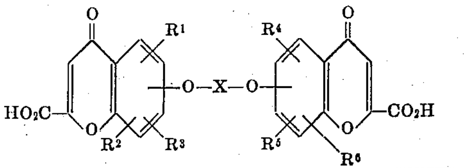
Primary Examiner—Daniel D. Horwitz
Attorney—Wenderoth, Lind & Ponack

[57] **ABSTRACT**

Compounds of the formula



wherein Z and Z' are hydroxy and Y and Y' are H, —$COCH_3$, or —COOR' (R' being an alkyl group) are used to prepare compounds of the formula



and therapeutically acceptable salts, esters and amides thereof, wherein R^1, R^2, R^3, R^4, R^5 and R^6 are the same or different and each is H or halogen, lower alkyl, hydroxy, lower alkoxy, substituted lower alkyl or substituted lower alkoxy, and X is a saturated or unsaturated, substituted or unsubstituted, straight or branched polymethylene chain which may be interrupted by one or more carbocyclic rings or oxygen-containing heterocyclic rings, oxygen atoms or carbonyl groups. The latter compounds are useful as inhibitors of certain antigen-antibody reactions, being particularly useful for the relief and prophylaxis of asthma.

4 Claims, No Drawings

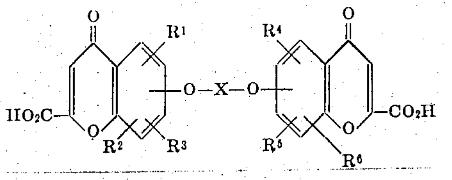
BIS-PHENOXY COMPOUNDS

This application is a divisional application of application Ser. No. 536,281, filed Mar. 22, 1966, now U. S. Pat. No. 3,419,578, and Ser. No. 765,722, filed July 30, 1968, the latter application being a divisional application of the former.

This invention is concerned with improvements in or relating to new chemical compounds and pharmaceutical compositions containing them.

It has now been found that certain new chromone derivatives, as hereinafter defined, possess special activity as inhibitors of the effects of certain types of antigen-antibody reaction, as evidenced, for example, by in vivo tests.

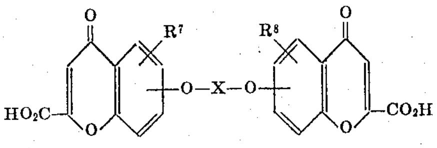
According to the invention, therefore, there are provided as new compounds bis-chromonyl compounds of the formula:



and functional derivatives thereof, in which R^1, R^2, R^3, R^4, R^5 and R^6 are the same or different and each is a hydrogen or halogen atom (e.g. a chlorine, bromine, iodine or fluorine atom), a lower alkyl (e.g. a methyl, ethyl, propyl, isopropyl, butyl or tertiaryl butyl group), hydroxy, lower alkoxy (e.g. a methoxy, ethoxy, propoxy, isopropoxy, butoxy or tertiary butoxy group) or substituted lower alkyl or lower alkoxy group, (for example a hydroxyloweralkoxy, loweralkoxyloweralkoxy, carboxyloweralkoxy, hydroxyloweralkyl or haloloweralkyl such as chloro-, bromo-, iodo- or fluoro-loweralkyl) and X is a saturated or unsaturated, substituted or unsubstituted, straight or branched polymethylene chain which may be interrupted by one or more carbocyclic rings or oxygen containing heterocyclic rings, (e.g. benzene, dioxan, tetrahydrofuran, or dihydropyran rings), oxygen atoms or carbonyl groups.

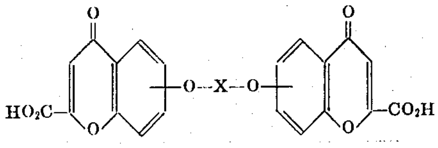
In general, it is preferred that not more than one of R^1 R^2 and R^3 and not more than one of R^4, R^5 and R^6 is other than hydrogen.

Accordingly a preferred embodiment of the invention is constituted by bis-chromonyl compounds of the formula:



and functional derivatives thereof, in which R^7 and R^8 are the same or are different and each is a hydrogen or halogen atom or an alkyl, hydroxy, alkoxy or substituted alkoxy group, and X has the meaning defined above.

Particularly preferred compounds according to the invention are those in which all of R^1, R^2, R^3, R^4, R^5 and R^6 are hydrogen and accordingly a further preferred embodiment of the invention is constituted by bis-chromonyl compounds of the formula:

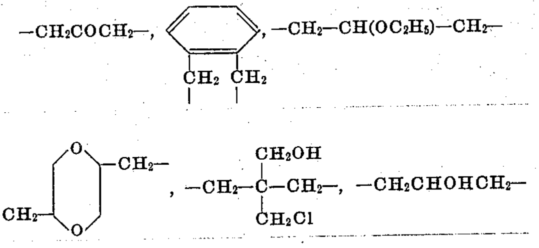


and functional derivatives thereof, in which X has the meaning defined above.

The group X may be any of a wide variety of groups. Thus for example, it may be a straight or branched saturated or unsaturated hydrocarbon chain. Further, X may be such a chain interrupted by one or more oxygen atoms, carbonyl groups or carbocyclic or heterocyclic rings and may be substituted by one or more halogen atoms (e.g. chlorine, bromine, iodine or fluorine atoms), or hydroxy or lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert.butoxy, etc) groups. Specific examples of the group X are groups of the formulae:

$$—(CH_2)_5—,\ —CH_2—CH{=}CH—CH_2—,$$

$$—CH_2CH_2CH—(CH_3)—CH_2CH_2—,\ —CH_2CH_2OCH_2CH_2—$$

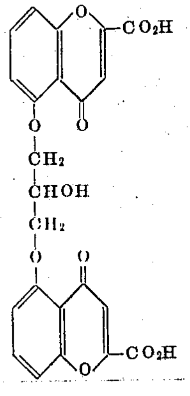


$$—CH_2CHOHCH_2OCH_2CHOHCH_2—, \text{etc.}$$

The group X is preferably a straight or branched hydrocarbon chain, which may be interrupted by one or more oxygen atoms, and contains from three to seven carbon atoms. Desirably such a chain is substituted by one or more hydroxyl groups, a particularly preferred chain being the 2-hydroxy-trimethylene chain ($—CH_2·CHOHCH_2—$).

The chain —O—X—O— may link different or corresponding positions on the chromone molecules.

A particularly preferred compound according to the invention, in view of its activity, is 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane of the formula:



and its functional derivatives.

Functional derivatives of the compounds according to the invention include salts, esters and amides of one or more of the carboxylic acid functions present and esters of any hydroxylic functions present.

Salts of the bis-chromonyl compounds which may be mentioned are salts with physiologically acceptable cations, for example, ammonium salts, metal salts such as alkali metal salts (e.g. sodium, potassium and lithium salts) and alkaline earth metal salts (e.g. magnesium and calcium salts) and salts with organic bases, e.g., amine salts such as piperidine, triethanolamine and diethylaminoethylamine salts.

Esters which may be mentioned include simple alkyl esters (e.g. methyl, ethyl, propyl, isopropyl, butyl and tertiary butyl esters) and amides which may be mentioned include simple amides (for example amides with ammonia and lower alkylamines such as methylamine, ethylamine etc) and more complex amides with amino acids such as glycine.

The new bis-chromonyl compounds according to the invention have been shown to inhibit the release and/or action of toxic products which arise from the combination of certain types of antibody and specific antigen, e.g., the combination of reaginic antibody with specific antigen. In man, it has been found that both subjective and objective changes which result from the inhalation of specific antigen by sensitized subjects are markedly inhibited by prior administration of the new bischromonyl compounds. Thus the new compounds are of great value in the prophylactic treatment of "extrinsic" allergic asthma. It has also been found that the new bis-chromonyl compounds are of value in the prophylactic treatment of so-called "intrinsic" asthma (in which no sensitivity to extrinsic antigen can be demonstrated).

It has also been found that in certain virus/antibody neutralization systems the new bis-chromonyl compounds enhance the neutralizing capacity of the antiserum, and thus the new compounds may find use in the treatment of viral infections.

According to a further feature of the invention, therefore, there is provided a pharmaceutical composition comprising a bis-chromonyl compound according to the invention, preferably in the form of a salt, in association with a pharmaceutical carrier or diluent. There is also provided a process for the manufacture of a pharmaceutical composition which comprises mixing a bis-chromonyl compound with a carrier or diluent.

The nature of the composition and the pharmaceutical carrier or diluent will, of course, depend upon the desired route of administration, i.e., orally, parenterally or by inhalation.

The compositions according to the invention are especially useful for the prophylactic treatment of asthma, i.e., the compositions are administered to the patient at regular intervals (e.g. 4–6 hourly) in order to inhibit the effects of asthmatic attacks from which the patient may suffer. When employed in this manner, the dosage of composition is preferably such that from 1–50 mg. of active compound are administered to the patient at each administration.

In general, for the prophylactic treatment of asthma, the compositions will be in a form suitable for administration by inhalation. Thus the compositions may comprise a suspension or solution of the active ingredient in water for administration by means of a conventional nebulizer. Alternatively the compositions may comprise a suspension or solution of the active ingredient in a conventional liquified propellant such as dichlorodifluoromethane or chlorotrifluorethane to be administered from a pressurized container. The compositions may also comprise the solid active ingredient diluted with a solid diluent, e.g. lactose, for administration from a powder inhalation device.

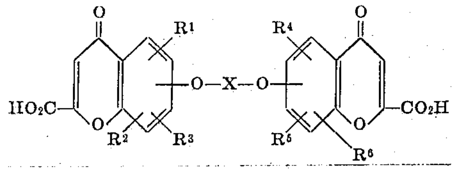
The pharmaceutical compositions according to the invention generally contain a minor proportion of bis-chromonyl compound and a major proportion of carrier or diluent. Thus, for example, the solutions for administration by a conventional nebulizer will comprise a dilute solution, e.g., about 0.5 percent, in sterile water, and compositions comprising suspensions or solutions in pressurized propellants will contain, for example, about 2 percent of the active bis-chromonyl compound. However, where the composition comprises the solid bis-chromonyl compound diluted with a solid diluent, the diluent may be present in less, equal or greater amount than the solid active ingredient, for example the diluent may be present in an amount of from 50 to 150 percent by weight of the solid active ingredient.

The invention also includes within its scope a method of inhibiting the effects of the antigen-antibody reaction which comprises the prior application to the area of the antigen-antibody mechanism a therapeutically effective amount of a bis-chromonyl compound according to the invention.

According to a particular embodiment, the invention is for a method of relieving or preventing allergic airway obstruction which comprises administering to the patient a therapeutically effective amount (e.g. 1–50 mg) at suitable intervals, of a bis-chromonyl compound according to the invention, particularly in the form of a salt.

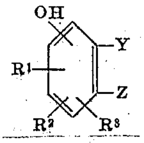
The new compounds according to the invention are prepared by linking together two chromone-2-carboxylic acids or precursors therefor.

According to a further feature of the invention, therefore, there is provided a process for the preparation of bis-chromonyl compounds of the formula:

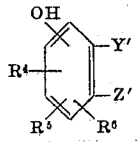


and functional derivatives thereof, in which R^1, R^2, R^3, R^4, R^5 and R^6 have the meanings defined above, which comprises reacting in one or more stages,

a. a compound of the formula:



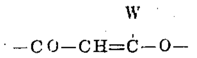
b. a compound of the formula:



and c. a compound of the formula:

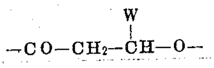
$$A-X'-B.$$

in which Z is a hydroxy group and Y is a hydrogen atom, a group $-COCH_3$ or a group $-COOR'$ (in which R′ is an alkyl group), or Y and Z together form a chain



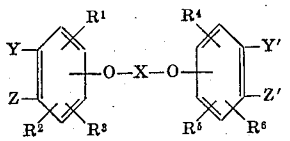
$$-CO-CH=\overset{W}{C}-O-$$

or a chain



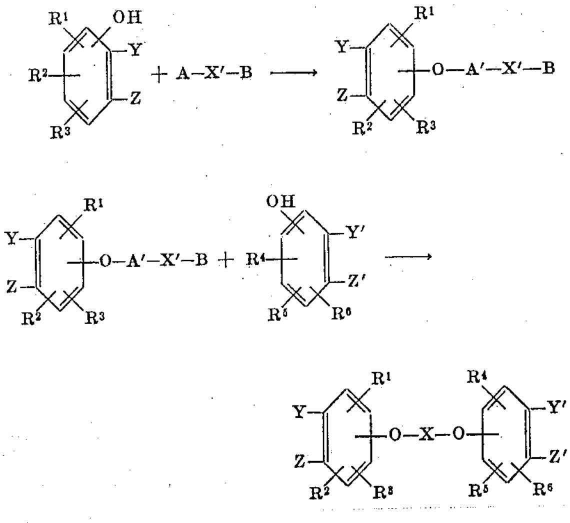
$$-CO-CH_2-\overset{W}{C}H-O-$$

(in which W is a carboxylic acid group or a functional derivative thereof or a group convertible to a carboxylic acid group or a functional derivative thereof), Y′ and Z′ have the same definition as Y and Z above and may be the same or different; and A and B are the same or different and each is a group capable of reacting with a hydroxyl group to form an ether linkage, or one of A and B is a group capable of being converted to such a reactive group; and X′ is such that the group $-A'-X'-B'-$ (in which A′ and B′ are the residues of A and B after the formation of ether linkages) has the same meaning as X; to form a compound of the formula:

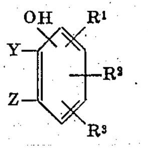


and, if necessary, intermediately or subsequently converting Y and Z and/or Y′ and Z′ to chains of the formula $-CO-CH=C(COOH)-O-$, or functional derivatives thereof.

As stated above, the process according to the invention may be carried out in one or more stages. Thus, it may be carried out in two stages as follows:



This procedure will generally be adopted when the two chromone moieties of the desired bis-chromonyl compound are different, i.e., when R^1, R^2 and R^3 are different from R^4, R^5, and R^6. In the two stage process, the groupings Y and Z or Y′ and Z′ may be modified at an intermediate stage but, in general, it is not preferred to follow this route. When the two chromone moieties of the desired bis-chromonyl compound are the same the reaction may be carried out in two stages, or preferably, if Y′ and Z′ have the same meanings as Y and Z, in one stage, i.e., by reaction of a compound of the formula:

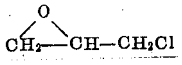


with a compound of the formula:

$$A-X'-B$$

When the reaction is carried out in two stages the compound $A-X'-B$ may be such that one of A and B is a group capable of being converted to an ether linkage forming group. When both A and B are ether linkage forming groups, the first stage of a two stage reaction will, of course, be carried out using substantially equimolecular proportions of the two compounds.

Examples of groups A and B capable of reacting with a phenolic hydroxyl group, such that an ether linkage is formed by X′ and the hydroxyl group, include halogen atoms, e.g., chlorine, bromine or iodine atoms, or other anion forming groups such as tosylate or methane sulphonate groups. Where the group A contains a hydroxy group beta to the subsequently formed ether linkage the group A or B may represent an epoxide group, giving rise to a residue A′ or B′ of $-CH_2-CHOH-$. The groups A and B may be the same or different; thus a compound $A-X'-B$ capable of yielding a 2-hydroxy-trimethylene linkage is the compound:



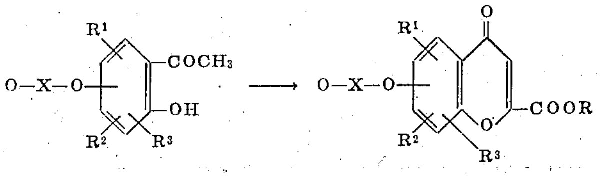
Groups capable of being converted to reactive groups such that an ether linkage may be subsequently formed include hydroxyl groups which may be converted to halogen substituents or other anion forming groups such as tosylate or methane sulphonate. The group A or B may alternatively be a vinyl group ($-CH=CH_2$) which may subsequently be converted to an epoxide or haldhydrin group. Thus, an example of a compound $A-X'-B$ which may be used to produce a 2-hydroxy-trimethylene linkage is allyl bromide.

The reaction between the chromone moiety or precursor therefor and the linking compound $A-X'-B$ will be carried out under the conditions normally employed for the formation of ether linkages. Thus, the reaction will generally be carried out in the presence of aqueous alkali or a solvent such as acetone or dioxan and at elevated temperature. Where the ether linkage formation is carried out by reaction of the aromatic hydroxy group and a compound $A-X'-B$ in which A and/or B is an anion forming group (e.g. halogen, methanesulphonate etc) the reaction is desirably ly carried out in the presence of an acid binding agent such as an alkali metal carbonate (e.g. sodium carbonate or potassium carbonate) or an organic acid binding agent such as pyridine, diethylaniline or triethylamine. Where A and/or B is an epoxide group the ether forming reaction may be conveniently carried out in the presence of a suitable catalyst, EE.G. in the presence of a quaternary ammonium hydroxide.

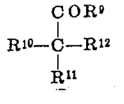
The conversion, if necessary, of Y and Z and/or Y′ and Z′ to the desired chain —CO—CH = C(COOH)—O— or functional derivative thereof will be carried out simultaneously if Y and Z are the same as Y′ and Z′ and in separate stages if Y and Z are not the same as Y′ and Z′. It is, however, generally preferred that Y and Z are the same as Y′ and Z′ since this reduces the number of chemical stages involved.

In the following description of methods of converting Y and Z to the desired chain —CO—CH = C(COOH)—O— or functional derivatives thereof reference will only be made to one chromone moiety but it will, of course, be understood that where Y and Z are the same as Y′ and Z′ the process will act simultaneously on both moieties.

A preferred process involves the conversion of the compound in which Y is a group —CO—CH_3 and Z is a hydroxy group (i.e., a substituted o-hydroxyacetophenone) to a chain —CO—CH = C(COOR)—O— (in which R is a hydrogen atom or an alkyl group); i.e.,



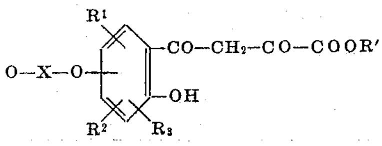
This reaction may be carried out by a number of routes. A preferred route involves the reaction of the o-hydroxyacetophenone with an oxalic acid derivative of the formula:



$$R^{10}-\overset{\displaystyle COR^{9}}{\underset{\displaystyle R^{11}}{C}}-R^{12}$$

in which R^9 is a halogen atom or a group —OR′ (in which R′ is an alkyl group), R^{10} and R^{11} are both halogen atoms and R^{12} is a group OR′ or R^{10} and R^{11} together represent an oxygen atom (= O) and R^{12} is a halogen atom or a group OR′.

Thus a particularly preferred process involves reaction of the ortho-hydroxy-acetophenone with a dialkyl oxalate, such as diethyl oxalate, preferably in the presence of a condensation agent such as an alkali metal alkoxide, e.g., sodium ethoxide, sodamide, metallic sodium or sodium hydride and conveniently in the presence of an organic solvent such as ether, dioxan, ethanol or benzene. This process goes through an intermediate of the formula:



where R′ is the alkyl group of the dialkyl oxalate, which intermediate may be cyclized directly by heating or may be isolated and cyclized by heating in a suitable solvent in the presence of a cyclization agent such as an acid.

When the oxalic acid derivative is of the formula:

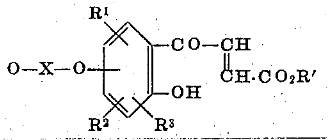
$$R'—O—C(Hal)_2—COOR''$$

in which R″ is an alkyl group, e.g. ethyl ethoxydichloroacetate, the reactants are desirably employed in substantially equimolecular proportions and the reaction is conveniently carried out in the presence of a metallic catalyst such as finely divided metallic platinum, palladium or ruthenium. When the oxalic acid derivative is of the formula:

$$Hal — CO — COOR'$$

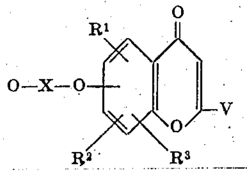
e.g. ethyl oxalyl chloride, the reaction is conveniently carried out in the presence of an acid binding agent. When the oxalate derivative is an exalyl halide such as oxalyl chloride, the reaction is suitably carried out in the presence of an organic solvent and in the presence of an acid binding agent.

The o-hydroxy-acetophenone may also be condensed with an ester of glyoxalic acid to give a compound of the formula:



which may then be oxidatively cyclized to the desired chromone-2-carboxylic acid. Non-oxidative cyclization gives rise to the corresponding chromanone which may be converted to the chromone as described below.

A different route for the formation of the desired chromonyl compound involves the conversion of Y and Z (when Y is —$COCH_3$ and Z is —OH) to an intermediate of the formula:



in which V is a group convertible to a carboxylic acid, or functional derivative thereof, and subsequent conversion of the group V to a carboxylic acid group or functional derivative thereof.

Examples of the group V are the nitrile group which may be hydrolyzed to a carboxylic acid group and groups such as methyl, hydroxymethyl, halomethyl (e.g. chloromethyl, bromomethyl, dichloromethyl, trichloromethyl), formyl, acetyl, vinyl and styryl groups, oxidizable or hydrolyzable to a carboxylic acid group.

The 2-methyl chromone may be prepared from the o-hydroxy-acetophenone by condensation with an alkyl acetate, in a similar manner to the condensation described above for the dialkyl oxalate.

The 2-methyl chromone also serves as an intermediate in the preparation of a number of other oxidizable derivatives. Thus, the 2-methyl chromone may be converted into the corresponding 2-halomethylchromone, e.g., by reaction with hydrogen chloride and manganese dioxide in boiling acetic acid to produce a 2-chloromethyl chromone or by reaction with bromine in acetic acid to yield the 2-bromomethylchromone. The 2-halomethyl chromone may be oxidized to the corresponding chromone-2-carboxylic acid, for example, with potassium permanganate, or may be hydrolyzed, using, for example, moist silver oxide, to give the 2-hydroxymethyl chromone which may then be oxidized to the chromone-2-carboxylic acid, for example, using chromium trioxide as oxidizing agent in the presence of acetic acid and at ambient temperature or below.

The 2-methyl chromone may further be reacted with p-nitrosodimethylaniline and the reaction product hydrolyzed with dilute mineral acid to give the corresponding 2-formyl-chromone which may be oxidized to the corresponding chromone-2-carboxylic acid using, for example, chromium trioxide as reagent.

Condensation of the 2-methyl-chromone with a benzaldehyde in the presence of a condensation catalyst gives the 2-styryl chromone which may be oxidized to the corresponding chromone-2-carboxylic acid, for example using potassium permanganate.

A number of the chromone derivatives, other than the 2-methyl chromone, convertible to the chromone-2-carboxylic acid may be prepared directly from the o-hydroxy-acetophenone.

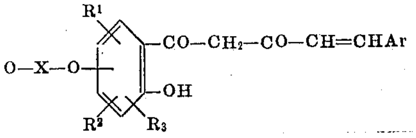
Thus, the 2-formyl chromone may be prepared by condensation of a dialkoxy acetate of the formula:

$$(R'O)_2 \cdot CH{-}COOR''$$

in which R′ and R″ have the meanings defined above, e.g., ethyl diethoxy acetate, with the o-hydroxy-acetophenone to yield an acetal which may subsequently be hydrolyzed, e.g., with dilute mineral acid, to the aldehyde, which may subsequently be oxidized to the carboxylic acid. hydrolyzed the chromone

The 2-formyl chromone may also serve as a starting point for the preparation of the 2-cyano chromone. Thus, the 2-formyl chromone may be reacted with hydroxylamine to yield the 2-oximino-chromone which may then be dehydrated to the 2-cyanochromone which may then be hydrolysed to the chromone-2-carboxylic acid or amide thereof under acid conditions.

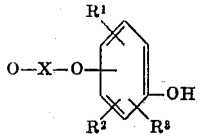
The 2-styryl chromone may be prepared from the o-hydroxy-acetophenone by reaction with sodium cinnamate and cinnamic anhydride (i.e. by the Kostanecki reaction) or by reaction with a cinnamoyl halide, e.g., cinnamoyl chloride, in the presence of an acid binding agent to yield the cinnamate ester of the o-hydroxy-acetophenone followed by treatment with a base, e.g. potassium carbonate, in the presence of an inert solvent such as toluene or benzene to give an alpha-diketone of the formula:



which is subsequently cyclized either by direct heating or by heating in the presence of a cyclization agent (Baker Venkataraman reaction).

The 2-vinyl chromone may likewise be prepared from the o-hydroxy-acetophenone by reaction with ethyl acrylate.

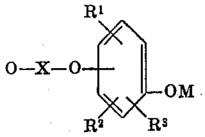
The compound in which Y is a hydrogen atom and Z is a hydroxyl group, i.e., the phenol of the formula:



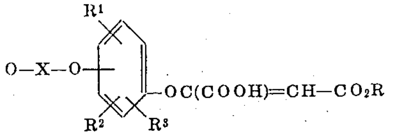
may be converted to the corresponding chromone-2-carboxylic acid by a number of methods.

For example, the chromone-2-carboxylic acid may be prepared by reaction of acetylene dicarboxylic acid or a dialkyl ester thereof, e.g., diethyl acetylene dicarboxylate, with the phenol or with an alkali metal phenate thereof.

Where the acetylene dicarboxylic acid or ester thereof is reacted with the alkali metal phenate, i.e., the compound of the formula:



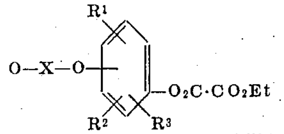
in which M is an alkali metal atom, the reaction is desirably carried out in the presence of an inert organic solvent or diluent to yield a fumarate of the formula:



which is then, if necessary after hydrolysis, cyclized to the desired chromone-2-carboxylic acid, for example by heating in the presence of a cyclization catalyst such as sulphuric acid. In a modification of this process the acetylene dicarboxylic acid or ester thereof is replaced by a halo-fumaric acid or an ester thereof, e.g., diethyl chlorofumarate, or by a dihalosuccinic acid or ester thereof.

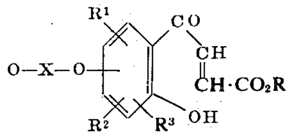
The chromone-2-carboxylic acid may also be prepared from the phenol by reaction with a compound such as ethyl ethoxalylacetate.

In another method the phenol may be esterified, e.g. with ethyl ethoxalyl chloride to give an ester of the formula:



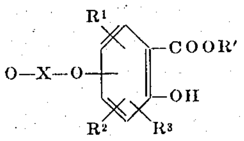
which may subsequently be cyclized in the presence of acetic acid or a derivative thereof (e.g., ethyl acetate or acetyl chloride) to give he desired chromone-2-carboxylic acid.

The phenol may alternatively be condensed with maleic anhydride to give a compound of the formula:



which may then be oxidatively cyclized to the desired chromone-2-carboxylic acid. Non-oxidative cyclization gives rise to the corresponding chromanone which may then be converted to the chromone as described below.

The compound in which Z is a hydroxyl group and Y is a group —COOR′ i.e. the substituted salicylic acid ester of the formula:

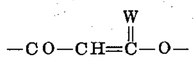


may be converted to the desired chromone-2-carboxylic acid by reaction with a pyruvate ester of the formula:

$$CH_3-CO-COOR'$$

if desired in the presence of a condensation agent such as an alkali metal alkoxide (e.g. sodium ethoxide), sodamide, metallic sodium or sodium hydride, and preferably in the presence of an organic solvent such as ethanol or dioxan.

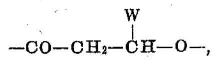
When Y and Z together form a chain



$$-CO-CH=\overset{W}{\overset{\|}{C}}-O-$$

in which W is the desired carboxylic acid group or functional derivative thereof, obviously no modification of Y and Z will be necessary. When W is group convertible to a carboxylic acid group, or a functional derivative thereof, it will have the same meaning as defined for V above and may be converted to the corresponding carboxylic acid group as described for V above.

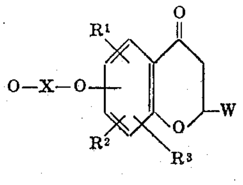
When Y and Z together form a chain



$$-CO-CH_2-\overset{W}{\overset{|}{C}}H-O-,$$

i.e., a chromanone, the group W will remain unchanged or be converted to a carboxylic acid group as necessary and further the chromanone will need to be dehydrogenated to the corresponding chromone; which dehydrogenation may be carried out either before or after any conversion of W.

The dehydrogenation of the chromanone of the formula:



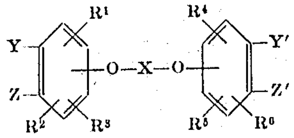
may, for example, be effected using selenium dioxide or other suitable dehydrogenating agents such as palladium black or chloranil.

Alternatively, dehydrogenation may be carried out by bromination followed by dehydrobromination. Thus, the chromanone may be brominated using N-bromosuccinimide in an inert solvent or by treatment with pyridinium perbromide in an inert solvent such as chloroform in the presence of a free radical catalyst such as benzoyl peroxide, to yield the 3-bromo derivative which may be subsequently dehydrobrominated.

The processes described above generally lead to the formation of the chromone-2-carboxylic acids as such or in the form of their esters. These may be readily converted to other functional derivatives, e.g., salts or amides, by conventional methods.

The majority of the intermediates produced by the linking of the two chromone moieties or precursors therefor are in themselves new.

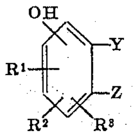
According to the invention, therefore, there are provided as new compounds, compounds of the formula:



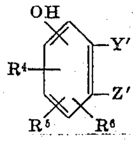
in which R^1, R^2, R^3, R^4, R^5B^6, X, Y, Z, Y′ and Z′ have the meanings defined above, provided that not more than one of Y and Z and Y′ and Z′ represents a chain —CO—CH C(COOH)—O— or a functional derivative thereof and further provided that when R^1, R^2, R^3, R^4, R^5 and R^6 are hydrogen and Y and Y′ are groups $COCH_3$ and Z and Z′ are hydroxyl groups, X is not a group $—CH_2—CHOH—CH_2—$ linking the two positions para to the groups Y and Y′.

This invention also provides a process for the preparation of the new intermediates which comprises reacting in one or more stages:

a. a compound of the formula:



b. a compound of the formula:



and (c) a compound of the formula:

$$A-X'-B$$

in which A and B have the meanings defined above.

In order that the invention may be well understood, the following examples are given by way of illustration only.

EXAMPLE 1

a. 1,3-Bis(2-acetyl-3-hydroxyphenoxy)propane

A mixture of 30.4 parts 2,6-dihydroxyacetophenone, 20.2 parts of 1,3-dibromopropane and 12.8 parts powdered potassium carbonate were heated under reflux in

200 parts by volume of acetone for 72 hours. The acetone solution was filtered and the solid residue was washed first with acetone and then with water. The combined acetone filtrate and washings were evaporated leaving an oil which, on being boiled with ether, gave pale yellow crystals. These were combined with the first obtained solid and extracted with refluxing isopropanol in a Soxhlet extractor for several days to obtain 16.1 parts of 1,3-bis(2-acetyl-3-hydroxyphenoxy)propane as almost colorless crystals melting between 184° and 185° C.

Analysis:

Found: C, 65.4; H, 5.68%

$C_{19}H_{20}O_6$ requires: C, 66.2; H, 5.81%

b. Diethyl ester of 1,3-bis(2-carboxychromon-5-yloxy)propane

A solution of 6.9 parts 1,3-bis(2-acetyl-3-hydroxyphenoxy) propane in 15 parts by volume of diethyl oxalate was added to a solution of 3 parts sodium in 30 parts by volume of ethanol and 50 parts by volume of benzene and the mixture was heated gently under reflux for 20 hours. It was then poured into a large volume of ether and the precipitated solid was filtered, washed with ether and dried. It was then dissolved in water and acidified to obtain a sticky solid. This was boiled with about 50 parts of ethanol containing a catalytic amount of hydrochloric acid for about 10 minutes, when crystals began to form. The solution was cooled and filtered to obtain 7.4 parts of solid melting between 178° and 180° C. This was recrystallized from 200 parts by volume of a 1:2 mixture of benzene and ethanol to obtain a first crop of 4.5 parts of the diethyl ester of 1,3-bis(2-carboxychromon-5-yloxy)propane, melting between 182° and 183° C.

Analysis:

Found: C, 63.2; H, 4.60%

$C_{27}H_{24}O_{10}$ requires: C, 63.7; H, 4.72%

c. Disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)propane

A suspension of 3 parts of the diethyl ester of 1,3-bis(2-carboxychromon-5-yloxy)propane in 50 parts by volume of boiling ethanol was treated with 11.6 parts by volume of 1.015N aqueous sodium hydroxide. Water was added until a clear solution was obtained. This was treated with charcoal, filtered and concentrated by boiling, with the occasional addition of more ethanol. On cooling 2.2 parts of colorless crystals of the disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)propane monohydrate more were obtained.

Analysis:

Found: C, 54.1; H., 2.86%

$C_{23}H_{14}Na_2O_{10}H_2O$ requires: C, 53.7; H., 3.11%

EXAMPLE 2

a. 1,3-Bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane

By the method of Example 1 (a) 10 parts of 2,6-dihydroxy-acetophenone, 4.6 parts potassium carbonate and 7.15 parts 1,3-dibromopropan-2-ol were reacted in acetone to obtain 3 parts of pure 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane as colorless crystals melting between 165° and 166° C.

Analysis:

Found: C, 63.5; H, 5.86%

$C_{19}H_{20}O_7$ requires: C, 63.3; H, 5.56%

b. 1,3-Bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane

To a solution of 970 parts of 2,6-dihydroxyacetophenone and 325 parts of epichlorohydrin in 2,500 parts of hot isopropanol was added, with stirring under reflux, a solution of 233 parts of 85 percent KOH in 2,500 parts of isopropanol and sufficient water (ca. 100 parts) to dissolve the solid. The mixture was heated, with stirring, under reflux for 48 hours. Half the solvent was then distilled off and 5000 parts of water were added. The mixture was cooled and the solid filtered off and washed with isopropanol and ether. It was then recrystallized from 12,500 parts of isopropanol to obtain a first crop of 380 parts and a second crop, after concentration, of 300 parts of 1,3-bis(2-acetyl- 3-hydroxyphenoxy)-2-hydroxypropane identical with that obtained in Example 2 (a) above.

c. Diethyl ester of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane

By the method of Example 1 (b) 4.6 parts of 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane were reacted with diethyl oxalate and the product cyclized to obtain 4.4 parts of pure diethyl ester of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane as pale yellow crystals melting between 180° and 182° from a mixture of benzene and petrol.

Analysis:

Found: C, 61.5; H, 4.61%

$C_{27}H_{24}O_{11}$ requires: C, 61.8; H, 4.57%

d. Disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane

By the method of Example 1 (c), 4 parts of the diethyl ester of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane were saponified to obtain 3.2 parts of the disodium salt tetrahydrate as colorless crystals from aqueous alcohol.

Analysis:

Found: C, 47.8; H, 3.8; Na, 7.7%

$C_{23}H_{14}Na_2O_{11}4H_2O$ requires: C, 47.3; H, 3.79; Na, 7.7%

e. 1,3-Bis(2-carboxychromon-5-yloxy)-2-hydroxypropane.

A solution of the disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane in water was acidified and the precipitate was recrystallized from ethanol plus ether to obtain 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane monohydrate as colorless crystals melting with decomposition between 216° and 217°.

Analysis:

Found: C, 56.7; H, 3.44%

$C_{23}H_{16}O_{11}H_2O$ requires: C, 56.8: H, 3.70%

Dehydration of the monohydrate in vacuo at 110° C gave the anhydrous acid melting between 241° and 242° C with decomposition.

f. Calcium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane

The disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane (0.8 parts) dissolved in the minimum volume of warm water was treated with a solution of 0.225 parts of calcium nitrate in a small volume of water, to obtain the sparingly soluble calcium salt. The mixture was cooled and filtered, and the solid was washed with cold water and dried at 110° C.

Analysis:

Found: Ca, 7.19%

$C_{23}H_{14}CaO_{11}3H_2O$ requires: Ca, 7.14%

g. Magnesium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane

A suspension of 2 parts of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane in 20 parts of water was treated with 0.36 parts of magnesium carbonate. The mixture was boiled with stirring until homogeneous, cooled, filtered and dried at 110° C to obtain 2.3 parts of the magnesium salt.

h. Dipiperidine salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane

A suspension of 2 parts of 1,3-bis(2-carboxychromon-5-yloxy) -2-hydroxypropane in 20 parts of water was treated with 0.7 part of piperidine. The mixture was warmed under reflux until a clear solution was obtained after which it was cooled and dehydrated by freeze-drying to obtain 2.8 parts of the dipiperidine salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane.

Analysis:

Found: C, 59.0; H, 6.12; N, 4.00%

$C_{33}H_{36}NO_{11}\cdot 2H_2O$ requires: C, 59.1; H, 5.67; N, 4.18%

EXAMPLE 3

a. 1,4-Bis(2-acetyl-3-hydroxyphenoxy)but-2-ene

By the method of Example 1 (a), 15.2 parts of 2,6-dihydroxy-acetophenone were condensed with 10.7 parts of 1,4-dibrombut-2-ene to obtain 6 parts of 1,4-bis(2-acetyl-3-hydroxyphenoxy)but-2-ene melting between 145° and 146° from acetone.

b. 1,4-Bis(2-carboxychromon-5-yloxy)but-2-ene

By the method of Example 1 (b), 5 parts of 1,4-bis(2-acetyl-3-hydroxyphenoxy)but-2-ene were condensed with diethyl oxalate to obtain 3 parts of the diethyl ester of 1,4-bis(2-carboxychromon-5-yloxy)but-2-ene as yellow crystals melting between 215° and 217° C from ethanol.

Analysis:

Found: C, 64.1; H, 4.69%

$C_{28}H_{24}O_{11}$ requires: C, 64.6; H, 4.6%

Saponification of 2 parts of the diethyl ester of 1,4-bis(2-carboxychromon-5-yloxy)but-2-ene by the method of Example 1 (c) gave 1.5 parts of the disodium salt.

Acidification of an aqueous solution of this sodium salt gave the free acid monohydrate, melting between 193° and 195°.

Analysis:

Found: C, 59.6;H3.56%

$C_{24}H_{16}O_{10}H_2O$ requires: C, 59.7; H, 3.73%

EXAMPLE 4

1,12-bis(2-carboxychromon-5-yloxy)-2,11-dihydroxy-4,9-dioxadodecane

A solution of 10 parts 2,6-dihydroxyacetophenone, 5.6 parts butane-1,4-diol diglycidyl ether and 0.1 part of 40 percent aqueous solution of benzyltrimethylammonium hydroxide in 14 parts dioxan was heated at 100° C in a sealed vessel for 60 hours. The dioxan was removed under reduced pressure leaving a thick yellow oil. This was extracted several times with boiling ether and the combined extracts were fractionally precipitated with petrol. The first fraction, which was about 5 parts of a clear yellow oil, could not be crystallized or distilled but had an infra-red spectrum consistent with that expected for 1,12-bis(2-acetyl-3-hydroxyphenoxy)-2,11-dihydroxy-4,9-dioxadodecane. This was condensed with diethyl oxalate by the method of Example 1 (b) to obtain 3 parts of the diethyl ester of 1,12-bis(2-carboxychromon-5-yloxy)-2,11-dihydroxy-4,9-dioxadodecane as an oil. This oil was stirred and warmed with a saturated aqueous solution of sodium bicarbonate until dissolved. The solution was filtered and acidified with dilute hydrochloric acid. The precipitate was dissolved in ethanol plus ethyl acetate, treated with charcoal, filtered and precipitated with petrol and the solid was recrystallized from acetone plus ether to obtain 1 part of pure 1,12-bis(2-carboxychromon-5-yloxy)-2,11-dihydroxy-4,9-dioxadodecane dihydrate as colorless crystals melting with decomposition at 80° C.

Analysis:

Found: C, 55.3; H, 5.24%

$C_{30}H_{30}O_{14}2H_2O$ requires: C, 55.3; H, 5.22%

1,12-Bis(2-carboxychromon-5-yloxy)-2,11-dihydroxy-4,9-dioxadodecane dihydrate (0.325 parts) was dissolved in a solution of 0.084 parts sodium bicarbonate in 100 parts water. The solution was filtered and freeze-dried to obtain 0.3 parts of the disodium salt tetrahydrate.

Analysis:

Found: C, 48.7; H, 4.75%

$C_{30}H_{28}Na_2o_{14}4H_2O$ requires: C, 49.3; H, 4.9%

EXAMPLE 5

a. 1,4-Bis(2-acetyl-3-hydroxyphenoxy)butane

By the method of Example 1 (a) 2,6-dihydroxyacetophenone was reacted with 1,4-dibromobutane to obtain 1,4-bis(2-acetyl-3-hydroxyphenoxy)butane melting between 219° and 221° C from benzene.

Analysis:

Found: C, 66.0; H, 6.0%

$C_{20}H_{22}O_6$ requires: C, 67.0; H, 6.2%

b. Diethyl ester of 1,4-bis(2-carboxychromon-5-yloxy)butane

By the method of Example 1 (b) 1,4-bis(2-acetyl-3-hydroxy-phenoxy)butane was condensed with diethyl oxalate to form the diethyl ester of 1,4-bis(2-carboxychromon-5-yloxy)butane melting between 195° and 199° C from a mixture of ethyl acetate and isopropanol.

Analysis:

Found: C, 62.4; H, 5.1%

$C_{28}H_{26}O_{10}H_2O$ requires: c, 62.3; H, 5.2%

c. 1,4-Bis(2-carboxychromon-5-yloxy)butane

The diethyl ester of 1,4-bis(2-carboxychromon-5-yloxy)butane was hydrolyzed by heating with aqueous sodium bicarbonate until dissolved, filtering and acidifying the solution. The precipitate was recrystallized from methanol to obtain pure 1,4-bis(2-carboxychromon-5-yloxy)butane monohydrate melting between 228° and 230° C.

Analysis:

Found: C, 58.6; H, 3.95%

$C_{24}H_{18}O_{10}H_2O$ requires: C, 59.5; H, 4.2%

This acid was dissolved in an equivalent amount of sodium bicarbonate solution and freeze-dried to obtain the disodium salt.

EXAMPLE 6

1,5-Bis(2-carboxychromon-5-yloxy)pentane

2,6-Dihydroxyacetophenone was reacted with 1,5-dibromopentane as in Example 1(a) to obtain 1,5-bis(2-acetyl-3-hydroxyphenoxy) pentane melting between 131° and 133° C from benzene.

Analysis:

Found: C, 67.4; H, 6.3%

$C_{21}H_{24}O_6$ requires: C, 67.7; H, 6.5%

This diketone was condensed with diethyl oxalate as in Example 1(b) to obtain the diethyl ester of 1,5-bis(2-carboxy-chromon-5-yloxy)pentane, melting between 150° and 152° C from ethanol.

Analysis:

Found: C, 64.6; H, 5.3%

$C_{29}H_{28}O_{10}$ requires: C, 64.8; H, 5.3%

The ester was hydrolyzed as in Example 5(c) to obtain the acid as a monohydrate melting between 226° and 228° C from ethanol.

Analysis:

Found: C, 60.3; H, 4.7%

$C_{25}H_{20}O_{10}H_2O$ requires: C, 60.2; H, 4.4%

The acid was subsequently converted to the disodium salt by the method of Example 5(c).

EXAMPLE 7

1,6-Bis(2-carboxychromon-5-yloxy)hexane

2,6-Dihydroxyacetophenone was reacted with 1,6-dibromohexane as in Example 1(a) to obtain 1,6-bis(2-acetyl-3-hydroxyphenoxy) hexane melting between 147.5° and 148.5° C from ethanol.

Analysis:

Found: C, 68.1; H, 6.7%

$C_{22}H_{26}O_6$ requires: C, 68.4; H, 6.8%

This diketone was condensed with diethyl oxalate by the method of Example 1(b) to obtain the diethyl ester of 1,6-bis(2-carboxychromon-5-yloxy)hexane melting between 154.5° and 155° C from ethanol.

Analysis:

Found: C, 65.0; H, 5.4%

$C_{30}H_{30}O_{10}$ requires: C, 65.4; H, 5.5%

The ester was hydrolyzed as in Example 5(c) to obtain the acid monohydrate melting between 228° and 230° C from dioxan.

Analysis:

Found: C, 60.2; H, 4.9%

$C_{26}H_{22}O_{10}H_2O$ requires: C, 60.9; H, 4.7%

The disodium salt of the acid was subsequently prepared as in Example 5 (c).

EXAMPLE 8

1,10-Bis(2-carboxychromon-5-yloxy)decane

2,6-Dihydroxyacetophenone was condensed with 1,10-dibromodecane as in Example 1 (a) to obtain 1,10-bis(2-acetyl-3-hydroxyphenoxy) decane melting between 102.5° and 104° C from ethyl acetate.

Analysis:

Found: C, 70.0; H, 7.4%

$C_{26}H_{34}O_6$ requires: c, 70.6; H, 7.7%

This diketone was reacted with diethyl oxalate as in Example 1 (b) to obtain the diethyl ester of 1,10-bis(2-carboxychromon-5-yloxy)decane melting between 146.5° and 148° C from ethanol plus dioxan.

Analysis:

Found: C, 67.4; H, 6.45%

$C_{34}H_{38}O_{10}$ requires: C, 67.3; H, 6.3%

The ester was hydrolyzed by boiling with aqueous sodium bicarbonate to obtain the sparingly soluble disodium salt which was recrystallized from water.

Analysis:

Found: C, 61.0; H, 5.2%

$C_{30}N_{28}Na_2O_{10}$ requires: 60.6; H, 4.7%

EXAMPLE 9

1,7-Bis(2-carboxychromon-5-yloxy)-2,6-dihydroxy-4-oxaheptane

2,6-Dihydroxyacetophenone was reacted with diglycidyl ether as in Example 4 to obtain 1,7-bis(2-acetyl-3-hydroxyphenoxy) 2,6-dihydroxy-4-oxaheptane melting between 129° and 131° C from ethyl acetate plus petrol.

Analysis:

Found: C, 60.4; H, 6.3%

$C_{22}H_{26}O_9$ requires: C, 60.8; H, 6.0%

This diketone was reacted with diethyl oxalate to obtain the bischromone diethyl ester as an oil which could not be crystallized, This ester was hydrolyzed as in Example 5 (c) to obtain 1,7-bis(2-carboxychromon-5-yloxy)-2,6-dihydroxy-4-oxaheptane monohydrate melting between 216° and 218° C.

Analysis:

Found: C, 55.6; H, 3.4%

$C_{26}H_{22}O_{13}H_2O$ requires: C, 55.7; H, 4.3%

The disodium salt was subsequently prepared as in Example 5 (c).

EXAMPLE 10

1,5-Bis(2-carboxychromon-5-yloxy)-3-oxapentane

2,6-Dihydroxyacetophenone was condensed with 2,2′-dibromo-diethyl ether, as in Example 1 (a) to obtain 1,5-bis(2-acetyl-3-hydroxyphenoxy)-3-oxapentane melting between 120.5° and 121,5° C from methanol.

Analysis:

Found: C, 63.5; H, 5.1%

$C_{22}H_{22}O_7$ requires: C, 64.1; H, 5.9%

This was condensed with diethyl oxalate as in Example 1 (b) to obtain the diethyl ester of 1,5-bis(2-carboxychromon-5-yloxy)-3-oxapentane melting between 129° and 131.5° C from methanol.

Analysis:

Found: C, 62.3; H, 4.9%

$C_{28}H_{28}O_{11}$ requires: C, 62.4; H, 4.9%

The ester was hydrolyzed as in Example 5 (c) to obtain the acid melting between 219° and 220° C from ethanol plus dioxan.

Analysis:

Found: C, 59.8; H, 3.9%

$C_{24}H_{18}O_{11}$ requires: C, 59.8; H, 3.8%

The disodium salt of the acid was subsequently prepared as in Example 5 (c).

EXAMPLE 11

1,4-Bis(2-carboxychromon-5-yloxy)-2,3-dihydroxybutane

2,6-Dihydroxyacetophenone was reacted with 1,2:3,4-bisepoxybutane as in Example 4 to obtain 1,4-bis(2-acetyl-3-hydroxyphenoxy)-2,3-dihydroxybutane, melting between 211° and 212° C from dioxan.

Analysis:

Found: C, 61.0; H, 5.7%

$C_{20}H_{22}O_8$ requires: C, 61.5; H, 5.7%

This was condensed with diethyl oxalate as in Example 1 (b) to obtain the diethyl ester of 1,4-bis(2-carboxychromon-5-yloxy)-2,3-dihydroxybutane melting between 224° and 226° C.

Analysis:

Found: C, 59.2; H, 4.6%

$C_{28}H_{26}O_{12}$ requires: C, 60.6; H, 4.7%

This was hydrolyzed by the method of Example 5 (c) to obtain the acid as a dihydrate melting between 260° and 262° C.

Analysis:

Found: C, 54.0; H, 3.7%

$C_{24}H_{18}O_{12}2H_2O$ requires: C, 54.0; H, 4.1%

This was subsequently converted to the disodium salt as in Example 5 (c).

EXAMPLE 12

1,4-Bis(2-carboxychromon-5-yloxy)-2-hydroxybutane

2,6-Dihydroxyacetophenone was condensed with 1-bromo-3,4-epoxybutane by boiling in acetone in presence of potassium carbonate to obtain 1,4-bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxybutane melting between 207.5° and 208.5° C from methanol.

Analysis:

Found: C, 63.4; H, 5.8%

$C_{20}H_{22}O_7$ requires: C, 64.2; H, 5.9%

This was condensed with diethyl oxalate as in Example 1 (b) to obtain the diethyl ester of 1,4-bis(2-carboxychromon-5-yloxy)-2-hydroxybutane melting between 216° and 217° C from a mixture of chloroform, ethyl acetate and petrol.

Analysis:

Found: C, 62.7; H, 5.2%

$C_{28}H_{26}O_{11}$ requires: C, 62.4; H, 4.9%

This was hydrolyzed as in Example 5 (c) to obtain the acid as a monohydrate melting between 226° and 227° C.

Analysis:

Found: C, 57.1; H, 3.9%

$C_{24}H_{18}O_{11}$ H_2O requires: C, 57.6; H, 4.0%

This was subsequently converted to the disodium salt as in Example 5 (c).

EXAMPLE 13

1,5-Bis(2-carboxychromon-7-yloxy)pentane

Ethyl 7-hydroxychromone-2-carboxylate was condensed with one half equivalent of 1,5-dibromopentane by heating in acetone in presence of potassium carbonate to obtain the diethyl ester of 1,5-bis(2-carboxychromon-7-yloxy)petane melting between 148° and 150° C from ethanol.

Analysis:

Found: C, 64.6; H, 5.3%

$C_{29}H_{28}O_{10}$ requires: C, 64.8; H, 5.3%

This ester was hydrolyzed as in Example 5 (c) to obtain the acid melting between 283° and 284° C.

Analysis:

Found: C, 61.8; H, 4.2%

$C_{25}H_{20}O_{10}$ requires: C, 62.4; H, 4.2%

The acid was subsequently converted to the disodium salt by the method of Example 5 (c).

EXAMPLE 14

1,10-Bis(2-carboxychromon-5-yloxy)-3,8-dioxa-4,7-dioxodecane

Ethyl 5-(2-hydroxyethoxy)chromone-2-carboxylate (1.4 parts) and 0.4 parts succinyl chloride were dissolved in chloroform and treated with 0.5 parts pyridine. The mixture was heated under reflux for 16 hours. The chloroform solution was washed with dilute hydrochloric acid, sodium carbonate solution and water and dried over sodium sulphate. The chloroform was distilled to leave an oil which was solidified by trituration with petrol. It was recrystallized from ethanol to obtain 0.2 parts of the diethyl ester of 1,10-bis(2-carboxychromon-5-yloxy)-3,8-dioxa-4,7-dioxodecane melting between 144° and 146° C.

Analysis:

Found: C, 60.5; H, 4.97%

$C_{32}H_{30}O_{14}$ requires: C, 60.2; H, 4.69%

EXAMPLE 15

1,5-Bis(2-carboxy-8-chlorochromon-5-yloxy)pentane

A mixture of 4.62 parts of 1,5-bis(2-acetyl-3-hydroxyphenoxy) pentane (from Example 6) and 2.7 parts of sulphuryl chloride in 300 parts of dry ether was stirred for 7 hours at room temperature. The solution was filtered and evaporated to dryness leaving a yellow solid. This was recrystallized from ether to obtain 2.36 parts of 1,5-bis(2-acetyl-4-chloro-3-hydroxyphenoxy)pentane as pale yellow prisms melting at 96° C.

This was condensed with diethyl oxalate as in Example 1 (b) to obtain the diethyl ester of 1,5-bis(2-carboxy-8-chlorochromon-5-yloxy)pentane melting between 162° and 164° C from ethanol.

Analysis:

Found: C, 57.7; H, 4.3%

$C_{29}H_{26}Cl_2O_{10}$ requires: C, 57.5; H, 4.3%

The ester was hydrolyzed as in Example 5 (c) to obtain the acid, melting at 244° C from ethanol.

Analysis:

Found: C, 54.2; H, 4.6; Cl, 12.9%

$C_{25}H_{18}Cl_2O_{10}$ requires: C, 54.7; H, 3.28; Cl, 12.9%

The acid was converted to the disodium salt by the method of Examples 5 (c).

EXAMPLE 16

a. 2-(2,3-Epoxypropoxy)-6-hydroxyacetophenone

To a mixture of 5.68 parts of 2,6-dihydroxyacetophenone, 10.3 parts of epichlorohydrin and 3 parts (by volume) of ethanol which was stirred and gently refluxed, was added slowly a solution of 2.58 parts of potassium hydroxide in 7 parts (by volume) of ethanol and 1 part (by volume) of water. The mixture was then stirred and refluxed for 1 hour, then after cooling an excess of water was added and the product was extracted into ether and the solution was dried over sodium sulphate. After removing the drying agent and the solvent 5 parts of a crude oil remained. This oil was extracted using hot petrol ether (b.p. 40°–60°) and on cooling yellow crystals of 2-(2,3-epoxypropoxy)-6-hydroxyacetophenone m.p. 61°–63° separated.

Analysis:

Found: C, 63.5; H, 5.7%

$C_{11}H_{12}O_4$ requires: C, 63.45; H. 5.8%

b. 1-(2-Acetyl-3-hydroxyphenoxy)-3-(4-acetyl-3-hydroxyphenoxy)-2-hydroxypropane.

A mixture of 5 parts of 2-(2,3-epoxypropoxy)-6-hydroxy-acetophenone, 3.8 parts of resacetophenone, 20 parts (by volume) of dioxan and 5 drops of trimethyl benzyl ammonium hydroxide solution were heated at 100° C in a sealed bottle overnight. After cooling the product crystallized out and was recrystallized from dioxan to yield 2 parts of 1-(2-acetyl-3-hydroxyphenoxy)-3-(4-acetyl-3-hydroxyphenoxy)-2-hydroxypropane melting between 182° and 185° C.

Analysis:

Found: C, 62.8; H, 5.4%

$C_{19}H_{20}O_7$ requires: C, 63.3; H, 5.6%

c. 2-(3-Chloro-2-hydroxypropoxy)-6-hydroxyacetophenone

A mixture of 10 parts of 2,6-dihydroxyacetophenone, 7 parts of epichlorohydrin in 18 parts (by volume) of dioxan and 5 drops of Triton B, was heated at 100° C in a sealed vessel for 2½ days. The solvent was then removed under reduced pressure and an excess of ether was added to the residue. The ether solution was decanted from the insoluble, washed with water (2 × 50 parts) and 2N sodium carbonate (3 × 25 parts). The solvent was removed after drying over sodium sulphate and the residue was purified by chromatography using an alumina column and ether as eluent. The oil was distilled to obtain 2-(3-chloro-2-hydroxypropoxy)-6-hydroxyacetophenone (6 parts) as a yellow oil b.p. 166°–8° at 1.5mm.

Analysis:

Found: C, 53.7; H, 5.26%

$C_{11}H_{13}C1O_4$ requires: C, 54.0; H, 5.32%

d. 1-(2-Acetyl-3-hydroxyphenoxy)-3-(4-acetyl-3-hydroxyphenoxy)-2-hydroxypropane

To the above chlorohydrin (6 parts) was added 3.8 parts of resacetophenone, 3.5 parts of anhydrous potassium carbonate and 50 parts (by volume) of dry acetone. This mixture was refluxed for 2 days. Then the insoluble material was filtered, after cooling, and stirred in water to remove inorganic material. Recrystallization of the residue from dioxan yielded 0.7 parts of 1-(2-acetyl-3-hydroxyphenoxy)-3-(4-acetyl-3-hydroxyphenoxy)-2-hydroxypropane melting between 182° and 185° C and identical with the product from (b) above. From the acetone filtrate a further 2 parts of this product were obtained.

e. 1-(2-Ethoxycarbonylchromon-5-yloxy)-3-(2-ethoxycarbonylchromon-7-yloxy)-2-hydroxypropane.

By the method of Example 1(b) 1-(2-acetyl-3-hydroxyphenoxy)-3-(4-acetyl-3-hydroxyphenoxy)-2-hydroxypropane was condensed with diethyl oxalate to form 1-(2-ethoxycarbonylchromon-5-yloxy)-3-(2-ethoxycarbonylchromon-7-yloxy)-2-hydroxypropane melting between 193° and 194.5° C from ethanol plus dioxan.

Analysis:

Found: C, 62.0; H, 4.3%

-hydroxypropane.

$C_{27}H_{24}O_{11}$ requires: C, 61.8; H, 4.6% F. 1-(2-Carboxychromon-5-yloxy)-3-(2-carboxychromon-7-yloxy)-2-hydroxypropene.

The ester from (e) above was hydrolyzed as in Example 5(c) to obtain the acid melting between 194° and 200° C with preliminary softening.

Analysis:

Found: C, 55.2; H, 3.96%

$C_{23}H_{16}O_{11}H_2O$ requires: C, 54.7; H, 3.9%

This acid was dissolved in an equivalent amount of sodium bicarbonate solution and freeze-dried to obtain the disodium salt.

EXAMPLE 17

a. 1-(2-Acetyl-3-hydroxyphenoxy)-5-(4-acetyl-3-hydroxyphenoxy)pentane

A mixture of 5.1 parts of 2,6-dihydroxyacetophenone, 7.7 parts of 1,5-dibromopentane, and 2.3 parts of anhydrous potassium carbonate in 100 parts (by volume) of anhydrous acetone was refluxed for 20 hrs. An examination of this mixture by thin layer chromatography showed unchanged 2,6-dihydroxy acetophenone, 1,5-bis(2-acetyl-3-hydroxyphenoxy)pentane and suspected 2-(5-bromopentyloxy)-6-hydroxyacetophenone to be present. The acetone solution was concentrated to half its volume and the residue was removed by filtration. After washing with water this residue yielded 1.9 parts of 1,5-bis(2-acetyl-3-hydroxyphenoxy)pentane. The filtrate was taken to dryness and chromatographed on an alumina column using ether as eluent. The 2-(5-bromo-pentyloxy)-6-hydroxyacetophenone came off in the first fractions, as confirmed by thin layer chromatography. Evaporation of these collected fractions yielded 5 parts as an oil which was used as follows without further purification. Thus a mixture of 2.4 parts of the crude oil, 1.2 parts of resacetophenone, 1 part of anhydrous potassium carbonate and 40 parts (by volume) of dry acetone was refluxed for 20 hrs. After cooling the acetone solution was filtered and evaporated to dryness. The residue was crystallized from methanol-water to yield 1.85 parts of 1-(2-acetyl-3-hydroxyphenoxy)-5-(4-acetyl-3-hydroxy-phenoxy)pentane melting between 91° and 91.5° C.

Analysis:

Found: C, 67.3; H, 6.7%

$C_{21}H_{24}O_6$ requires: C, 67.7; H, 6.5%

b. 1-(2-Ethoxycarbonylchromon-5-yloxy)-5-(2-ethoxycarbonylchromon-7-yloxy)pentane.

By the method of Example 1(b) 1-(2-acetyl-3-hydroxyphenoxy)-5-(4-acetyl-3-hydroxyphenoxy)pentane was condensed with diethyl oxalate to yield the desired product crystallizing from ethanol and melting between 149° and 152° C.

Analysis:

Found: C, 64.1; H, 5.3%

$C_{29}H_{28}O_{10}$ requires: C, 64.9: H, 5.3%

c. 1-(2-Carboxychromon-5-yloxy)-5-(2-carboxychromon-7-yloxy)pentane

To 1.0012 parts of the above bis-ester in 30 parts (by volume) of methanol was added an amount of 0.969N sodium hydroxide in methanol just sufficient for the ester hydrolysis. This mixture was then heated on the steam-bath for ½ hr, the solvent was distilled off and the residue was taken up in water and filtered, the filtrate was then acidified with dilute hydrochloric acid. The solid which separated proved difficult to filter and was, therefore, separated from the liquors by centrifuging, washing twice with water and recentrifuging. The 1-(2-carboxy-chromon-5-yloxy)-5-(2-carboxychromon-7-yloxy)pentane (0.25 parts) was crystallized from ethanol and had a melting point between 249° and 251° C with preliminary softening.

Analysis:

Found: C, 60.3; H, 4.4%

$C_{25}H_{20}O_{10}\cdot H_2O$ requires: C, 60.2; H, 4.45%

This acid was dissolved in an equivalent amount of sodium bicarbonate solution and freeze-dried to obtain the disodium salt.

EXAMPLE 18

a. 1,3-Bis(2-acetyl-3-hydroxy-5-methylphenoxy)-2-hydroxypropane.

To a solution of sodium ethoxide in ethanol (from 0.83 parts of sodium and 20 parts by volume of ethanol) was added a solution of 12 parts of 2,6-dihydroxy-4-methylacetophenone and 3.34 parts of epichlorohydrin in 10 parts (by volume) of ethanol. The resulting mixture was stirred and refluxed for 4 hrs; after cooling 250 parts of water were added and the solid was isolated by filtration. Crystallization of this solid from ethanol yielded 4.15 parts of 1,3-bis(2-acetyl-3-hydroxy-5-methylphenoxy)-2-hydroxypropane melting between 185° and 186° C.

Analysis:

Found: C, 64.1; H, 6.3%

$C_{21}H_{24}O_7$ requires: C, 6.49; H, 6.2%

b. 1,3-Bis(2-carboxy-7-methylchromon-5-yloxy)-2-hydroxypropane.

By the method of Example 1(b) the above compound was condensed with diethyl oxalate to yield 1,3-bis(2-ethoxycarbonyl-7-methylchromon-5-yloxy)-2-hydroxypropane crystallizing from ethanol as colorless needles melting between 194° and 196° C. The ester was hydrolyzed as in Example 5(c) to obtain the acid as the monohydrate crystallizing from aqueous dioxan and melting between 240° and 241° C.

Analysis:

Found: C, 58.3; H, 4.4%

$C_{25}H_{20}O_{11}\cdot H_2O$ requires: C, 58.4; H, 4.3%

The acid was subsequently converted to the disodium salt by the method of Example 5(c).

EXAMPLE 19

a. 1,3-Bis(2-acetyl-4-ethyl-3-hydroxyphenoxy)-2-hydroxypropane.

2,6-Dihydroxy-3-ethylacetophenone was condensed with epichlorohydrin by the method of Example 18(a) to yield 1,3-bis(2-acetyl-4-ethyl-3-hydroxyphenoxy)-2-hydroxypropane melting between 135° and 137° C (from ethanol).

Analysis:

Found: C, 66.7; H, 6.9%

$C_{23}H_{28}O_7$ requires: C, 66.3; H, 6.8%

b. 1,3-Bis(2-carboxy-8-ethylchromon-5-yloxy)-2-hydroxypropane.

The above compound was condensed with diethyl oxalate as in Example 1(b) to obtain 1,3-bis(2-ethoxycarbonyl-8-ethylchromon-5-yloxy)-2-hydroxypropane melting between 159° and 161° C (from ethanol).

This ester was hydrolyzed as in Example 5(c) to obtain the acid as the dihydrate crystallizing from ethanol and melting between 193° and 194° C.

Analysis:

Found: C, 57.5; H, 4.9%

$C_{27}H_{24}O_{11}\cdot 2H_2O$ requires: C, 57.85; H, 5.0%

The disodium salt was then prepared as in Example 5(c).

EXAMPLE 20

The activity of the new bis chromonyl compounds has been evaluated by the antigen inhalation test on human volunteers who suffer from specific allergic asthma. The degree of asthma provoked by the inhalation of an antigen to which the volunteers are sensitive can be measured by repeated estimation of the increase of air-way resistance.

A suitably designed spirometer was used to measure the forced expiratory volume at one second (F.E.V.$_{1.0}$), and hence the changes in the air way resistance. The anti-allergic activity of a compound is estimated from the difference between the maximum per cent F.E.V.$_{1.0}$ reduction following control and test provocations after drug administration conducted under identical experimental conditions.

Thus:

$$\text{Percent protection} = 100\times\left[\frac{\begin{array}{c}\text{Av. max.\% F.E.V.}_{1.0}\\ \text{fall control shock}\end{array} - \begin{array}{c}\text{Max.\% F.E.V.}_{1.0}\\ \text{fall test shock}\end{array}}{\text{Av. max.\% F.E.V.}_{1.0}\ \text{fall control shock}}\right]$$

The compounds under test were administered as an aerosol by inhalation for five minutes, two hours before challenge with antigen. The compounds for administration were dissolved in sterile water at a concentration of 0.5 percent and aerosolized from a Wright nebulizer operating at 10 liters/minute air flow, giving a total weight of drug aerosolized of 5 mg. The following table shows the protection obtained with a number of the new bis-chromonyl compounds.

Compound Under Test	% Protection
Disodium salt of 1,5-bis(2-carboxychromon-5-yloxy)-pentane	30 – 35
	pentane.
Disodium salt of 1,7-bis(2-carboxychromon-5-yloxy)-2, 6-dihydroxy- 4-oxaheptane.	25 – 30
Disodium salt of 1,4-bis(2-carboxychromon-5-yloxy)butane:	45 – 50
Disodium salt of 1,4-bis(2-carboxychromon-5-yloxy)-2, 3dihydroxy-butane.	40 – 45
Disodium salt of 1,4-bis(2-carboxychromon-5-yloxy)-2-hidroxy-butane.	50 – 55
Disodium salt of 1,4-bis(2-carboxychromon-5-yloxy)-but-2-ene.	45 – 50
Disodium salt of 1,10-bis(2-carboxychromon-5-yloxy-decane.	35 – 40
Disodium salt of 1,6-bis(2-carboxychromon-5-yloxy)-hexane.	45 – 50
	hexane.
Disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane.	65 – 70
Disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)-propane.	40 – 45
Disodium salt of 1,5-bis(2-carboxy-8-chlorochromon-5-yloxy)pentane	20 – 25
Disodium salt of 1,5-bis(2-carboxychromon-6-yloxy-pentane.	20 – 25
Disodium salt of 1,5-bis(2-carboxychromon-7-yloxy)-pentane.	45 – 50
Disodium salt of 1,3-bis(2-carboxychromon-7-yloxy)-2-hydroxypropane.	40 – 45
Disodium salt of 1,3-bis(2-carboxy-8-ethylchromon-5-yloxy)-2-hydroxypropane.	20 – 25
Disodium salt of 1,2-bis(2-carboxychromon-5-yloxymethyl)-benzene.	30 – 35
Disodium salt of 1-(2-carboxychromon-5-yloxy)-3-(2-carboxychomon-7-yloxy)- 2-hydroxypropane.	45 – 50
Disodium salt of 1,3-bis(2-carboxychromon-6-yloxy)-2-hydroxypropane.	40 – 45
Disodium salt of 1,3-bis(2-carboxy-8-methylchromon-7-yloxy)- 2-hydroxypropane.	15 – 20
Disodium salt of 1-(2-carboxycychromon-5-yloxy)-3-(2-carboxy-8ethyl-chromon-5-yloxy)∓'-hydroxy-propane.	25 – 30
Dipotassium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-chloromethyl-2-hydroxymethylpropane.	40 – 45
Disodium salt of 1,5-bis(2-carboxychromon-5-yloxy)-3-methylpentane.	20 – 25
Disodium salt of 1-(2-carboxychromon-5-yloxy)-3-(2-carboxy-'32-hydroxy-propane.	35 – 40
	121 2
Disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)-acetone.	30 – 35
Disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-ethoxypropane.	30 – 35

Clinical investigations of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane in the form of its disodium salt, hereinafter referred to as compound A, have been carried out on volunteers having clinical evidence of allergic asthma. In the case of some of the volunteers this asthma was identified as extrinsic asthma, i.e., was provoked by a specific antigen; the majority of the volunteers, however, were classified as suffering from intrinsic asthma, i.e., did not respond to a large number of skin and aerosol provocation tests.

In the case of the volunteers suffering from extrinsic asthma it was possible to assess the degree of protection afforded quantitatively using the test procedure described above.

In the case of subjects suffering from intrinsic asthma the therapeutic effect of compound A could be assessed subjectively and by objective tests of lung function.

The results of the clinical investigations may be summarized as follows:

1. Inhalation of compound A in doses of 1–20 mg. repeated at 4 to 8 hour intervals is well tolerated; no side effects or other evidence of toxicity being observed during a continuous trial period of 5 months.
2. The therapeutic effect of compound A may be apparent in 4 hours but increases for several days with continued therapy, reaching a maximum in 1 to 2 weeks. A dose of 2–6 mg. 4 to 6 hourly induces a significant improvement as shown by objective tests of lung function in mild cases.

In more severe cases, doses of up to 20 mg. at 4 to 6 hourly intervals are required to produce a significant improvement.

In quantitative objective tests it has been found that compound A, administered in a dose of 20 mg. gives up to 84 percent protection 2 hours after administration, up to 70 percent protection 4 hours after administration, and noticeable protection, e.g. about 20 percent protection 18 hours after administration.

Subjective improvement usually includes:

a. Reduction of chest tightness;

b. Increased tolerance to exercise; and

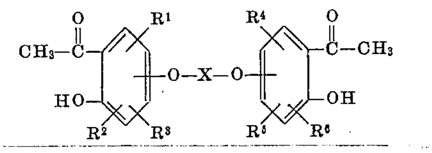
c. Reduced sputum volume and cough.

Withdrawal of therapy with compound A was followed by a relapse within 48 hours in severe cases or after 7–14 days in mild cases.

The acute i.v. toxicity of compound A, in rats, has been found to be low; i.e., the LD_{50} is at least 1000 mg/Kg.

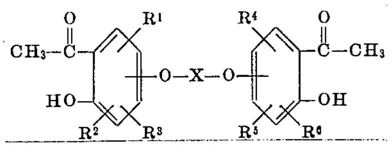
What is claimed is:

1. A compound of the formula



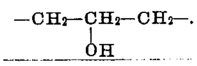
in which R^1, R^2, R^3, R^4, R^5 and R^6 are each selected from the group consisting of hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, hydroxylower alkyl, haloloweralkyl, hydroxyloweralkoxy, and loweralkoxyloweralkoxy and X is selected from the group consisting of straight and branched, saturated and unsaturated hydrocarbon chains which are uninterrupted or interrupted by a member selected from the group consisting of benzene, oxygen and carbonyl and are unsubstituted or substituted by a member of the group consisting of halogen or hydroxy and lower alkoxy, with the proviso that when R^1, R^2, R^3, R^4, R^5 and R^6 are hydrogen, X is not the group $—CH_2—CHOH—CH_2—$ linking the two positions para to the acetyl groups.

2. A compound of the formula



in which R^1, R^2, R^3, R^4, R^5 and R^6 are each selected from the group consisting of hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, hydroxylower alkyl, haloloweralkyl, hydroxyloweralkoxy, and loweralkoxyloweralkoxy, and X represents a saturated hydrocarbon chain which is unsubstituted or which is substituted by a member of the group consisting of halogen, hydroxy or lower alkoxy with the proviso that when R^1, R^2, R^3, R^4, R^5 and R^6 are hydrogen, X is not a group $—CH_2—CHOH—CH_2—$ linking the two positions para to the acetyl groups.

3. A compound according to claim 2 wherein X represents the group



$$—CH_2—\underset{OH}{\underset{|}{CH}}—CH_2—.$$

4. A compound according to claim 3, said compound being 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-hydroxypropane.

* * * * *

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,686,320 Dated August 22, 1972

Inventor(s) COLIN FITZMAURICE and THOMAS BRIAN LEE

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In column 1, below "[21] Appln. No.: 762,638" insert the following:

--[30] Foreign Application Priority Data

March 25, 1965	Great Britain	12626/65
December 9, 1965	Great Britain	52414/65--

Signed and sealed this 13th day of November 1973.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

RENE D. TEGTMEYER
Acting Commissioner of Patents